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Assessing changes in incubation period, serial interval, and generation time of SARS-CoV-2 variants of concern: a systematic review and meta-analysis

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Abstract

Background After the first COVID-19 wave caused by the ancestral lineage, the pandemic has been fueled from the continuous emergence of new SARS-CoV-2 variants. Understanding key time-to-event periods for each emerging variant of concern is critical as it can provide insights into the future trajectory of the virus and help inform outbreak preparedness and response planning. Here, we aim to examine how the incubation period, serial interval, and generation time have changed from the ancestral SARS-CoV-2 lineage to different variants of concern.

Methods We conducted a systematic review and meta-analysis that synthesized the estimates of incubation period, serial interval, and generation time (both realized and intrinsic) for the ancestral lineage, Alpha, Beta, and Omicron variants of SARS-CoV-2.

Results Our study included 280 records obtained from 147 household studies, contact tracing studies, or studies where epidemiological links were known. With each emerging variant, we found a progressive shortening of each of the analyzed key time-to-event periods, although we did not find statistically significant differences between the Omicron subvariants. We found that Omicron BA.1 had the shortest pooled estimates for the incubation period (3.49 days, 95% CI: 3.13–4.86 days), Omicron BA.5 for the serial interval (2.37 days, 95% CI: 1.71–3.04 days), and Omicron BA.1 for the realized generation time (2.99 days, 95% CI: 2.48–3.49 days). Only one estimate for the intrinsic generation time was available for Omicron subvariants: 6.84 days (95% CrI: 5.72–8.60 days) for Omicron BA.1. The ancestral lineage had the highest pooled estimates for each investigated key time-to-event period. We also observed shorter pooled estimates for the serial interval compared to the incubation period across the virus lineages. When pooling the estimates across different virus lineages, we found considerable heterogeneities ($I^2 > 80\%$; I^2 refers to the percentage of total variation across studies that is due to heterogeneity rather than chance), possibly resulting

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from heterogeneities between the different study populations (e.g., deployed interventions, social behavior, demographic characteristics).

Conclusions Our study supports the importance of conducting contact tracing and epidemiological investigations to monitor changes in SARS-CoV-2 transmission patterns. Our findings highlight a progressive shortening of the incubation period, serial interval, and generation time, which can lead to epidemics that spread faster, with larger peak incidence, and harder to control. We also consistently found a shorter serial interval than incubation period, suggesting that a key feature of SARS-CoV-2 is the potential for pre-symptomatic transmission. These observations are instrumental to plan for future COVID-19 waves.

Keywords COVID-19, Variants of concern, Incubation period, Serial interval, Realized generation time, Intrinsic generation time, Systematic review, Meta-analysis

Background

As of April 12, 2023, the COVID-19 pandemic has resulted in more than 762 million reported cases and 6.8 million reported deaths [1]. Since the first detection of SARS-CoV-2 (the virus causing COVID-19) in Wuhan, China, in December 2020, the virus has started to evolve, and several variants of SARS-CoV-2 have been identified. Five of them were classified as variants of concern (VOCs): Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529) [2]. Alpha and Delta were particularly successful at spreading around the globe, causing major waves of infections and associated hospitalizations since late 2020 and early 2021 [3, 4]. In late 2021, Omicron was first detected in South Africa and spread more rapidly than all other VOCs, causing massive outbreaks worldwide albeit with a lower associated burden due to high vaccination levels [2, 5, 6]. As of August 2023, Omicron subvariants are dominant worldwide.

Knowledge of the transmission dynamics of SARS-CoV-2 VOCs is vital for understanding the epidemiology of COVID-19 and establishing effective control measures. In this context, three key indicators are the incubation period, serial interval, and generation time (Fig. 1). First, the incubation period is the interval between an individual's time of infection and symptom onset; this indicator has crucial public health implications as, for instance, it can be used for (i) defining the length of the quarantine period and (ii) designing clinical trials (e.g., to monitor participants for disease signs after exposure). Second, the serial interval is the interval between symptom onset of the infector and symptom onset of the infectee(s); the serial interval is relevant, for example, for (i) defining contact tracing protocols (e.g., for determining where and from whom an individual may have contracted the pathogen anticipate who that person might have infected, and determining the timeframe for potential secondary infections) and (ii) evaluating the effectiveness of interventions (i.e., a lengthening serial interval might indicate reduced transmission, while a shortening or consistent serial interval may suggest ongoing transmission despite interventions). Third, the generation time is the interval between the infector's time of infection and the infectee(s)'s time of infection; the generation time is crucial for (i) determining the speed of transmission of an epidemic outbreak (short generation time indicates rapid spread), and (ii) informing infectious disease models (as they rely on estimates of the generation time to simulate successive generations of infections). It is important to note that the generation time encompasses a non-linear combination of the latent period (time interval from infection to start of infectiousness) and infectious period (time interval from start of infectiousness to end of infectiousness) [7], as these two time periods may not be independent, and infectiousness can be variable over time [8, 9]. Moreover, it is important to stress that the distributions of the generation time and serial interval can be substantially different, especially in the presence of pre-symptomatic transmission, as it is the case for COVID-19. For instance, the distribution of the serial interval is generally symmetric and includes negative values; on the contrary, the distribution of the generation time is generally skewed, and the support of the distribution is strictly positive. Thus, it is crucial to have separate estimates of the distributions of the serial interval and generation time.

While many epidemiological investigations have estimated the incubation period, serial interval, and generation time for the VOCs, these indicators can be affected by a variety of factors related to the specific epidemiological situation of each study as well as deployed interventions [10–14]. Moreover, individual characteristics such as age, medical history, and immunity status can affect an individual's immune response to the virus, thereby affecting the length of the incubation period, viral shedding, and onset of disease [15, 16]. For these reasons, it is essential to combine these estimates to provide a more comprehensive picture of these indicators for the different VOCs. Previously, Du et al. reported that the Omicron variant had the shortest incubation period, followed

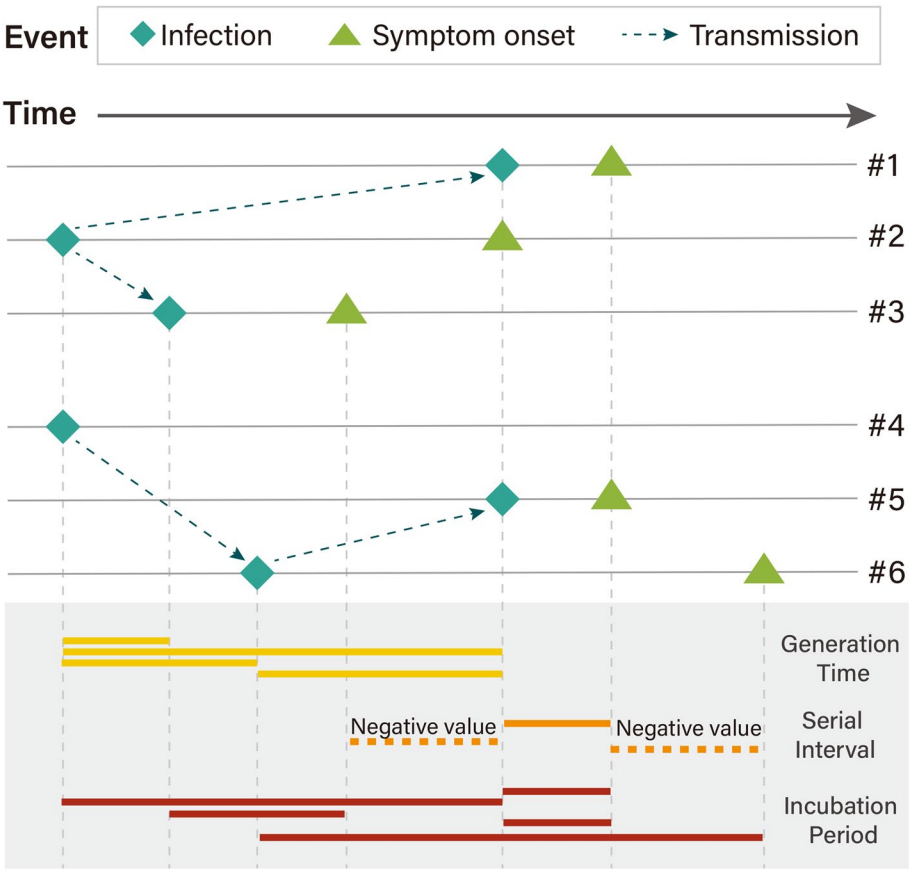

Fig. 1 Illustrative example of individual observations of the incubation period, serial interval, and generation time. The top part of the figure shows two hypothetical transmission chains as well as the dates of infection and symptom onset (if any) of infected individuals. Each row corresponds to a study participant (#1–#6). The bottom part of the figure shows the estimated individual values of the incubation period, serial interval, and generation time

by the Delta variant and ancestral lineage [17]. Additionally, they observed a shorter serial interval for both the Delta and Omicron variants compared to the ancestral lineage. Wu et al. observed a gradual decrease in the incubation period of COVID-19 from the Alpha variant to the Omicron variant with the evolution of mutant strains [16]. Madewell et al. observed that serial interval estimates for Delta and Omicron were shorter than ancestral SARS-CoV-2 variants, and more recent Omicron subvariants had even shorter serial intervals [18]. However, estimates need to be updated as more studies have been published since these meta-analyses have been conducted, especially regarding Omicron subvariants. Moreover, the previous meta-analyses did not include the generation time, nor did they analyze the co-evolution of the incubation period, serial interval, and generation time over different phases of the COVID-19 pandemic. As SARS-CoV-2 continues to mutate, systematically monitoring and comparing changes in these fundamental epidemiological indicators can provide insights into their possible future trajectory, thus providing invaluable insights for outbreak preparedness and response planning.

Methods

Search strategy

We conducted a systematic search following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (see PRISMA checklist) [19]. We searched for studies published in English on three peer-reviewed databases (PubMed, Embase, and Web of Science) and five preprint servers (medRxiv, bioRxiv, Europe PMC, SSRN, and arXiv) using predefined search terms (Additional file 1: Table S1). All searches were conducted on March 28, 2023.

Inclusion and exclusion criteria

Studies were included if they satisfied the following criteria: (1) provided at least one summarized statistic (e.g., central tendency and dispersion) for the incubation

period, serial interval, or generation time; (2) relied on data from a contact tracing study, a household study or a study where epidemiological links were known.

We excluded studies as follows: (1) were meta-analyses and reviews, study protocols, media news, commentaries, or the full text was unavailable (e.g., conference abstract); (2) SARS-CoV-2 variant/sub-variant or study period not reported; (3) carried out analysis with sample size less than five; (4) were non-human studies; (5) methods were not described.

Outcome measures

The outcome variables were incubation period, serial interval, and generation time. We further divided the generation time into two categories: intrinsic and realized. The intrinsic generation time represents the generation time that would be observed in a fully connected infinitely large susceptible population in the absence of interventions and behavioral change. The realized generation time refers to the generation time that is observed in field condition and is thus affected by specific features of the study population (e.g., interventions, individual behaviors, analyzed social settings) [20–22].

Data extraction

Study screening and data extraction were performed independently by authors YP.W. and X.X., and inconsistencies were reconciled together with a third author, Y.Z. For eligible studies, we extracted all summary statistics related to the outcomes of interest, including mean, median, interquartile range (IQR), range, standard deviation, quantiles, 95% confidence interval (CI), and 95% credible interval (CrI). In addition, we collected descriptive data on the authors, article's title, journal, date of publication, study location (country or region), date of the study period, total number of study subjects, variant type, and methods used for estimating key time-to-event intervals.

Quality assessment

Two authors (Z.H. and Y.Z.) independently carried out the quality assessment of the included literature. The quality assessment scale was adapted from the Newcastle–Ottawa quality assessment questions (Additional file 1: Table S2) [23]. Disagreements between the two reviewers were resolved together with a third author, X.X.

Data analysis

We described the central tendency (mean or median) and dispersion measure (range, IQR, 95% CI, or 95% CrI) for incubation period, serial interval, and generation time for the different VOCs via a forest plot. For studies reporting both mean and median, we preferred the mean estimates since most studies reported mean. For dispersion measures, we preferred 95% CI/CrI, followed by IQR and range. If CI/CrI was not provided, but sample size, standard deviation, or parametric distribution were provided, the adjusted confidence interval was calculated using the following formula as in references [16, 17]:

$$95\%\mathrm{CI} = \mathrm{mean} \pm 1.96 \times \frac{sd}{\sqrt{n}}$$

Next, we conducted a meta-analysis for different SARS-CoV-2 lineages and subvariants of the Omicron variant. The random-effects models were employed for all the pooling analyses, as they are more robust for small sample sizes. For studies reporting only the median and its associated dispersion measure, the corresponding mean, and 95% CI were approximated using methods described in Luo et al. [24]. If a study did not include a measure of central tendency or dispersion, the study was included in the review, but not in the meta-analysis. These methods were implemented using R function *metagen* from package *meta* [25]. The pooled average estimates with 95% CI were shown in forest plots. Then, we used the Wilcoxon test to assess the significance of the differences between the incubation periods, serial intervals, and generation times of the ancestral lineage, Alpha, Delta, Omicron variants, and subvariants of Omicron.

Publication bias was assessed using a funnel plot and Egger's test. A 2-sided $P < 0.05$ was considered statistically significant. All analyses were performed in R (version 4.1.0.). This review was not registered.

Results

Search results

A total of 25,929 studies were identified based on our search strategy. After excluding 3,263 duplicated studies and an additional 22,424 articles via screening titles and abstracts, 242 articles were assessed for eligibility through a meticulous review of the full article. As per the inclusion/exclusion criteria, 147 studies were included in our analysis [9, 10, 12, 13, 21, 22, 26–166], 7 of which were from preprint platforms. The specific reasons for excluding other 95 studies can be found in Additional file 1: Table S3 [11, 16, 17, 23, 87, 167–256]. Among the included studies, 92 studies provided incubation period estimates, 98 studies provided serial interval estimates, and 21 studies provided generation time estimates (Fig. 2). Sixty-three studies reported more than one outcome; 18 studies provided estimates for more than one virus lineage.

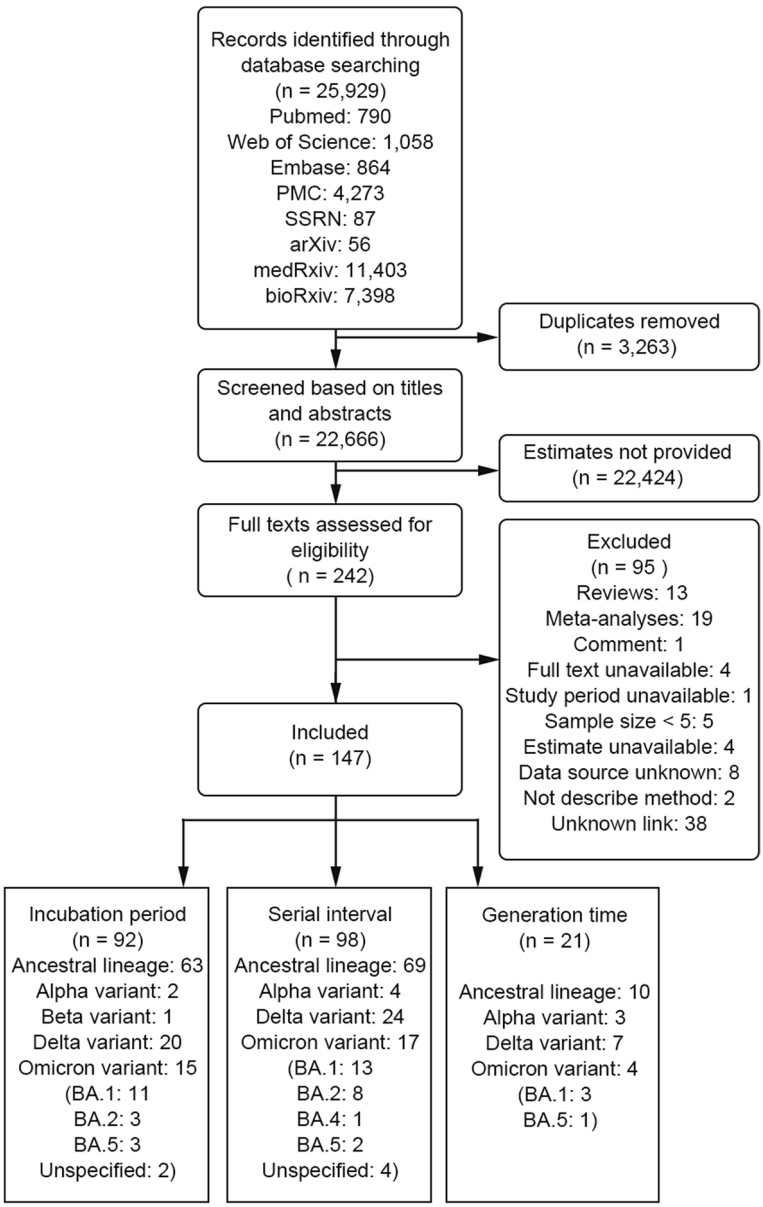

Fig. 2 Study flow diagram

Study characteristics

We extracted 280 records for the focus key time-to-event periods from 147 included studies. Each record contained at least one summary statistic of central tendency and dispersion measure of the outcome variable(s). Three countries provided 11 records for the Alpha variant: 5 from Italy, 4 from the UK, 1 from Japan, and 1 from Germany. France was the only country to provide a record for the Beta variant. A total of 59 records were obtained for the Delta variant from 12 countries: 23 from China, 10 from the Netherlands, 5 from the UK, 4 from Italy, 4 from Japan, 4 from South Korea, 3 from Singapore, 2 from Spain, 1 from Germany, 1 from Belgium, 1 from Australia and 1 from Ireland. For Omicron BA.1, a total of 33 records were provided from 11 countries, including 10 from the Netherlands, 6 from China, 4 from Italy, 3 from South Korea, 2 from Japan, 2 from Singapore, 2 from Spain, 1 from the UK, 1 from Germany, 1 from Belgium and 1 from Norway. For Omicron BA.2, a total of 11 records were provided from 4 countries, including 8 from China, 1 from Singapore, 1 from the UK, and 1 from Germany. China was the only country to provide a record for Omicron BA.4. For Omicron BA.5, a total of

6 records were provided from 3 countries, including 4 from China, 1 from the UK, and 1 from Japan.

We identified 111 (39.6%) records for incubation period from 92 studies. Sixty-nine (62.2%) records focused on the ancestral lineage, 2 (1.8%) on Alpha variant, 1 (0.9%) on Beta variant, 20 (18.0%) on Delta variant, 11 (9.9%) on Omicron BA.1, 3 (2.7%) on Omicron BA.2 and 3 (2.7%) on Omicron BA.5.

For serial intervals, we obtained 137 (48.9%) records from 98 studies. Seventy-one (51.8%) records included focused on the ancestral lineage, 4 (2.9%) on Alpha variant, 29 (21.2%) on Delta variant, 17 (12.4%) on Omicron BA.1, 8 (5.8%) on Omicron BA.2, 1 (0.7%) on Omicron BA.4, and 2 (1.5%) on Omicron BA.5.

For the generation time, 32 (11.4%) records from 21 studies were included in our analysis, among them were 27 records for the realized generation time and 5 records for intrinsic generation time. For realized generation time, 11 (40.7%) studies focused on the ancestral lineage, 3 (11.1%) on Alpha variant, 8 (29.6%) on Delta variant, 4 (14.8%) on Omicron BA.1 and 1 (3.7%) on Omicron BA.5. For intrinsic generation time, 2 (40%) on Alpha variant, 2 (40%) on Delta variant, and 1 (20%) on Omicron BA.1.

Quality assessment (Additional file 1: Table S4 [9, 10, 12, 13, 21, 22, 26–32, 34, 37–40, 42–60, 62–65, 67–71, 73, 74, 76, 78–86, 89, 90, 92–94, 97–99, 101–107, 109–115, 117–121, 123–128, 130, 131, 133, 136–139, 141–153, 155–161, 164–166]) indicated that 1 study provided a precise exposure window for cases and identification of the potential infector(s). Sixty-eight studies included a well-characterized cohort of individuals that were comparable with the population and provided precise estimates for the symptom onset window for themselves and their potential infector(s).

Incubation period

The ancestral lineage had the largest pooled mean incubation period (6.5 days, 95% CI: 5.88–7.12 days), followed by the Alpha variant (4.92 days, 95% CI: 4.53–5.30 days), Delta variant (4.63, 95% CI: 4.11–5.15 days), Omicron BA.2 (4.06 days, 95% CI: 3.18–4.93 days), Omicron BA.5 (3.81 days, 95% CI: 2.01–5.61 days), and Omicron BA.1 (3.49 days, 95% CI: 3.13–4.86 days) (Fig. 3, Additional file 1: Fig. S1 [9, 12, 21, 26, 28, 30–32, 34, 38–40, 42, 43, 47, 51, 52, 58–60, 62, 63, 65, 67, 70, 73, 74, 76, 78, 80, 81, 83, 85, 86, 92, 97, 98, 103–107, 109–115, 117–119, 130, 131, 133, 136–139, 142, 143, 155, 156, 165, 166]). Two studies did not specify the Omicron subvariant, and their pooled mean was 3.29 days (95% CI: 2.98–3.59 days); by pooling the estimates of the Omicron subvariants, the mean incubation period was 3.63 days (95% CI: 3.25–4.02 days). Only one study reported an estimate for the incubation period of the Beta variant (median: 4.5 days, IQR: 2–7 days). Delta, Omicron BA.1, Omicron BA.2 and Omicron BA.5 had significantly shorter incubation periods than the ancestral lineage (the p-values were 0.001, < 0.001, 0.023, and 0.050 for Delta, Omicron BA.1, Omicron BA.2, and Omicron BA.5, respectively; the sample sizes were 47, 14, 10, 3, and 3 for the ancestral lineage, Delta, Omicron BA.1, Omicron BA.2, and Omicron BA.5, respectively). Omicron BA.1 had significantly shorter incubation periods than Alpha and Delta (the p-values were 0.030 and 0.002 for Alpha and Delta, respectively). There was no significant difference between the other groups, which may be due to the small sample sizes. Our results suggested no potential publication bias in the included studies (p-value: 0.120) (Additional file 1: Fig. S2 [9, 12, 21, 26, 28, 30–32, 34, 38–40, 42, 43, 47, 51, 52, 58–60, 62, 63, 65, 67, 69, 70, 73, 74, 76, 78, 80, 81, 83, 85, 86, 92, 97, 98, 103–107, 109–115, 117–119, 130, 131, 133, 136–139, 142, 143, 155, 156, 165, 166]).

Serial interval

The ancestral lineage had the largest pooled mean serial interval (4.82 days, 95% CI: 4.5–5.14 days), followed by the Delta variant (3.59 days, 95% CI: 3.26–3.92 days), Alpha variant (3.47 days, 95% CI: 2.52–4.41 days), Omicron BA.2 (3.3 days, 95% CI: 2.92–3.68 days), Omicron BA.1 (3.21 days, 95% CI: 2.94–3.48 days), and Omicron BA.5 (2.37 days, 95% CI: 1.71–3.04 days) (Fig. 4, Additional file 1: Fig. S3 [9, 10, 12, 13, 21, 27–31, 34, 37–39, 44–51, 53, 54, 56, 57, 59, 60, 63, 64, 67, 68, 71, 76, 79, 81–84, 89, 90, 93, 94, 98, 99, 106, 109, 110, 119–121, 123, 124, 126–128, 131, 133, 136–139, 141, 142, 144–153, 156–158, 160, 161, 164–166]). Five studies did not specify the Omicron subvariant, and their pooled mean was 3.71 days (95% CI: 2.93–4.49 days); by pooling the estimates of the Omicron subvariants, the mean incubation period was 3.19 days (95% CI: 2.95–3.43 days). A significantly shorter serial interval was found for each lineage compared to the ancestral lineage (p-values: 0.024, < 0.001, < 0.001, < 0.001, 0.026 for Alpha, Delta, Omicron BA.1, Omicron BA.2, and Omicron BA.5, respectively; the sample sizes were 60, 4, 23, 16, 8, and 2 for the ancestral lineage, Alpha, Delta, Omicron BA.1, Omicron BA.2, and Omicron BA.5, respectively). There was no significant difference between the other groups. Our results suggested no potential publication bias in the included studies (p-value: 0.700) (Additional file 1: Fig. S4 [9, 10, 12, 13, 21, 27–31, 34, 37–39, 44–51, 53, 54, 56, 57, 59, 60, 63, 64, 67, 68, 71, 76, 79, 81–84, 89, 90, 93, 94, 98, 99, 106, 109, 110, 119–121, 123, 124, 126–128, 131, 133, 136–139, 141, 142, 144–153, 156–158, 160, 161, 164–166]).

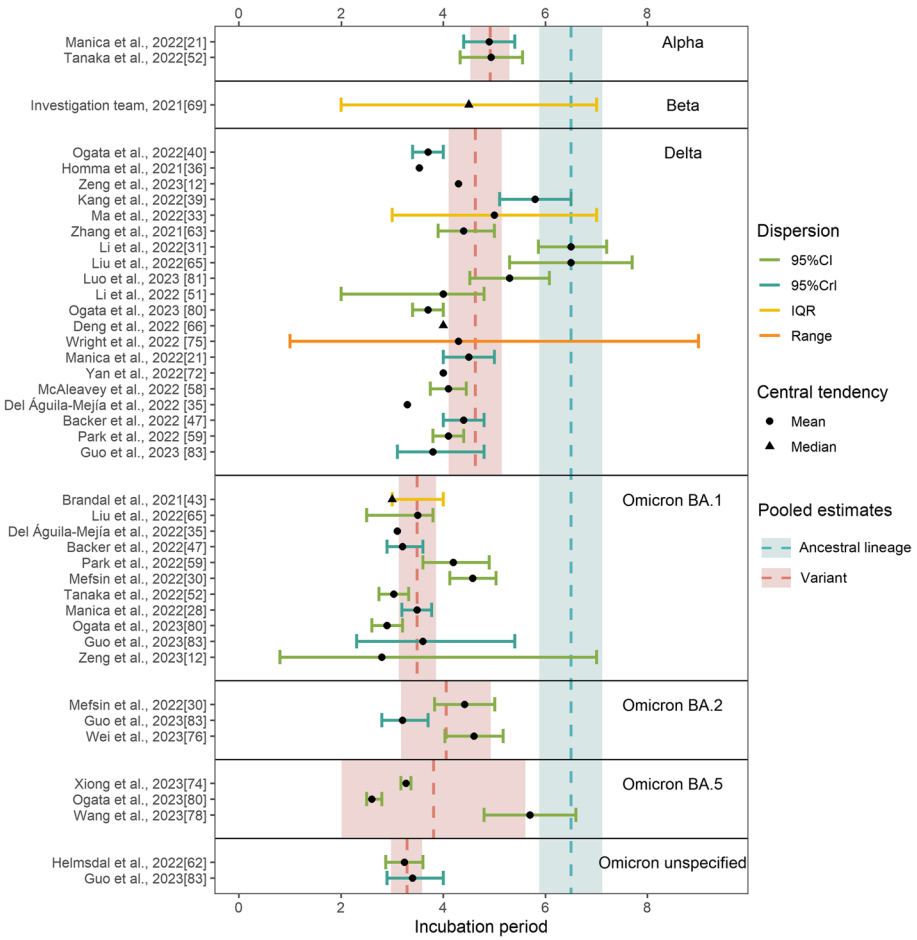

Fig. 3 The reported estimates of the incubation period. The blue vertical dotted line and rectangle correspond to the pooled mean estimate and its 95% CI of the ancestral lineage, respectively. The red vertical dotted line and rectangle in different strata denote the pooled mean estimates and their 95% CI of corresponding variants, respectively. Black points and triangles represent mean estimates and median estimates, respectively. The horizontal segments indicate CI (green), CrI (light blue), IQR (yellow), and range (orange)

Generation time

For the realized generation time, the ancestral lineage had the largest pooled mean generation time (4.95 days, 95% CI: 4.3–5.61 days), followed by the Alpha variant (4.35 days, 95% CI: 3.91–4.8 days), Delta variant (3.65 days, 95% CI: 3.25–4.05 days), and Omicron BA.1 (2.99 days, 95% CI: 2.48–3.49 days) (Fig. 5, Additional file 1: Fig. S5 [9, 21, 22, 28, 30, 55, 59, 63, 81, 101–104, 125, 142, 159]). Regarding the Omicron variant of all subvariants, the mean realized generation time was estimated to be 2.96 days (95% CI: 2.54–3.38 days). The realized generation times for the Delta and Omicron BA.1 were significantly shorter than the ancestral lineage (p-values: 0.021, 0.011 for Delta and Omicron BA.1, respectively; the sample sizes were 9, 6, 4 for the ancestral lineage, Delta, and Omicron BA.1, respectively). The central tendency of the realized generation time subsequently decreased by 16.1% from Alpha to Delta (p-value: 0.048), and there was no significant difference between the ancestral lineage and Alpha (p-value: 0.354; the sample size was 3 for Alpha), Alpha and Omicron BA.1 (p-value: 0.057), and Delta and Omicron BA.1 (p-value: 0.134). Our results suggested no potential publication bias in the included studies (p-value: 0.806) (Additional file 1: Fig. S6 [9, 21, 22, 28, 30, 55, 59, 63, 78, 81, 101–104, 125, 142, 159]).

For the intrinsic generation time, we obtained a pooled mean estimate of 5.86 days (95% CI: 5.47–6.26 days) for the Alpha variant based on two studies and 5.67 days (95% CI: 3.79–7.55 days) for the Delta variant based on two studies (Fig. 6, Additional file 1: Fig. S7 [21, 22]). Only one study (for Italy) reported an estimate for the Omicron variant: 6.84 days (95% CrI: 5.72–8.60 days). There was no significant difference between Alpha and Delta (p-value: 1).

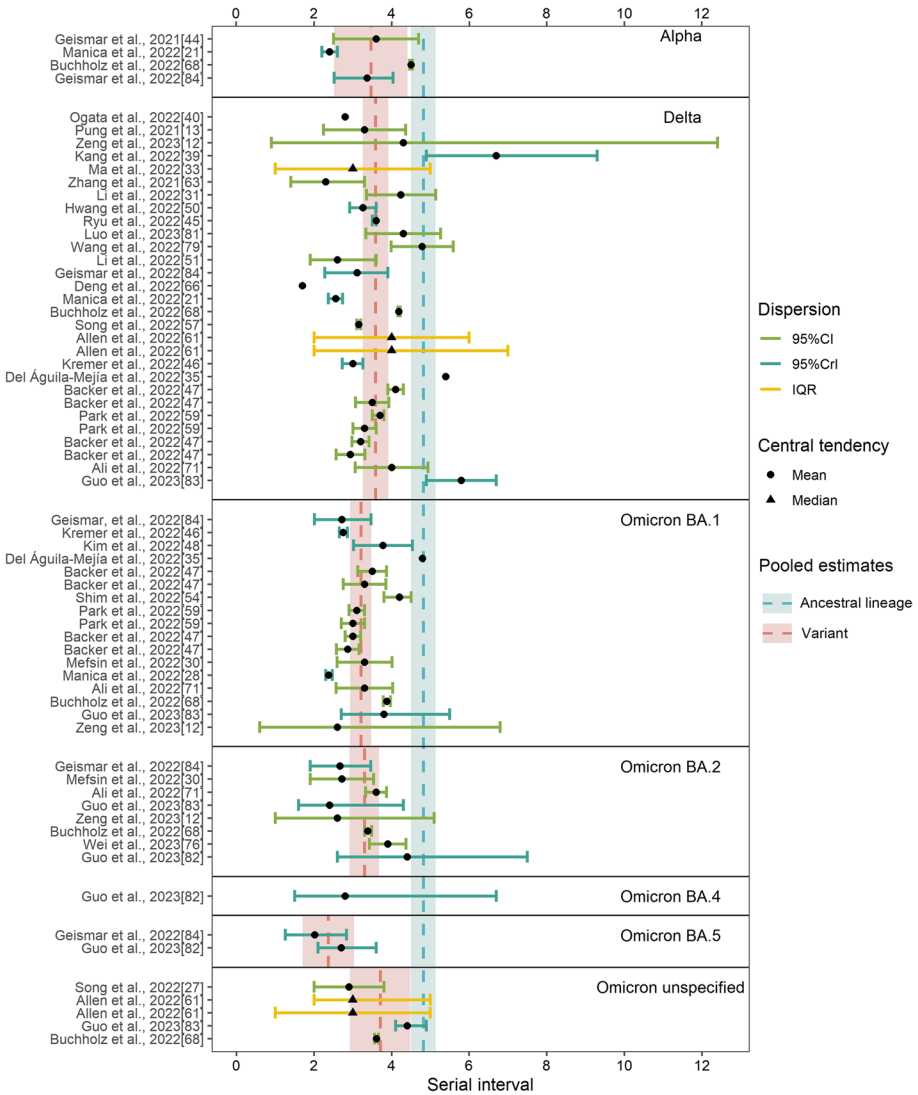

Fig. 4 The reported estimates of the serial interval. The blue vertical dotted line and rectangle correspond to the pooled mean estimate and its 95% CI of the ancestral lineage, respectively. The red vertical dotted line and rectangle in different strata denote the pooled mean estimates and their 95% CI of corresponding variants, respectively. Black points and triangles represent mean estimates and median estimates, respectively. The horizontal segments indicate CI (green), CrI (light blue), and IQR (yellow)

Discussion

Our study revealed a progressive shortening of each of the analyzed key time-to-event periods, although we did not find statistically significant differences between the Omicron subvariants. We found that Omicron BA.1 had the shortest pooled estimates for the incubation period (3.49 days, 95% CI: 3.13–4.86 days), Omicron BA.5 for the serial interval (2.37 days, 95% CI: 1.71–3.04 days), and Omicron BA.1 for the realized generation time (2.99 days, 95% CI: 2.48–3.49 days). Only one estimate for the intrinsic generation time was available for Omicron subvariants: 6.84 days (95% CrI: 5.72–8.60 days) for Omicron BA.1. The ancestral lineage had the highest pooled estimates for each investigated key time-to-event period. Our results were comparable to those of Galmiche et al. who reported SARS-CoV-2 incubation period was notably reduced in omicron cases compared with all other variants of concern [257]. These findings suggest that the incubation period, serial interval, and realized generation times of COVID-19 became shorter over the course of the pandemic.

The majority of the studies included in our analysis provided estimates for the incubation period (92 studies) and serial interval (98 studies), while only 21 studies provided estimates for the generation time. This suggests that estimates for serial interval and incubation period

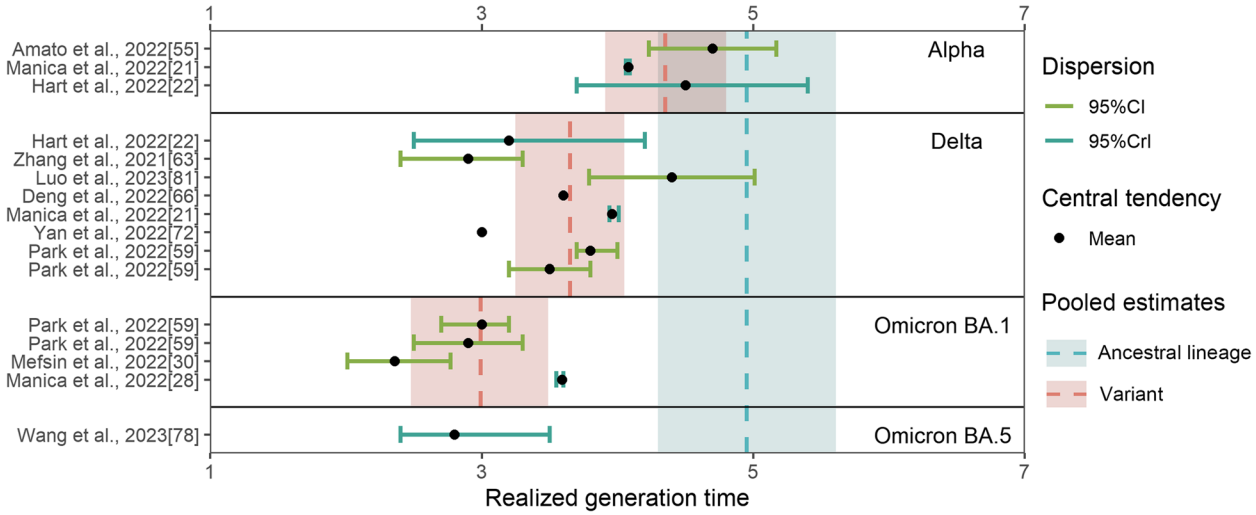

Fig. 5 The reported estimates of the realized generation time. The blue vertical dotted line and rectangle correspond to the pooled mean estimate and its 95% CI of the ancestral lineage, respectively. The red vertical dotted line and rectangle in different strata denote the pooled mean estimates and their 95% CI of corresponding variants, respectively. Black points and triangles represent mean estimates and median estimates, respectively. The horizontal segments indicate CI (green) and CrI (light blue)

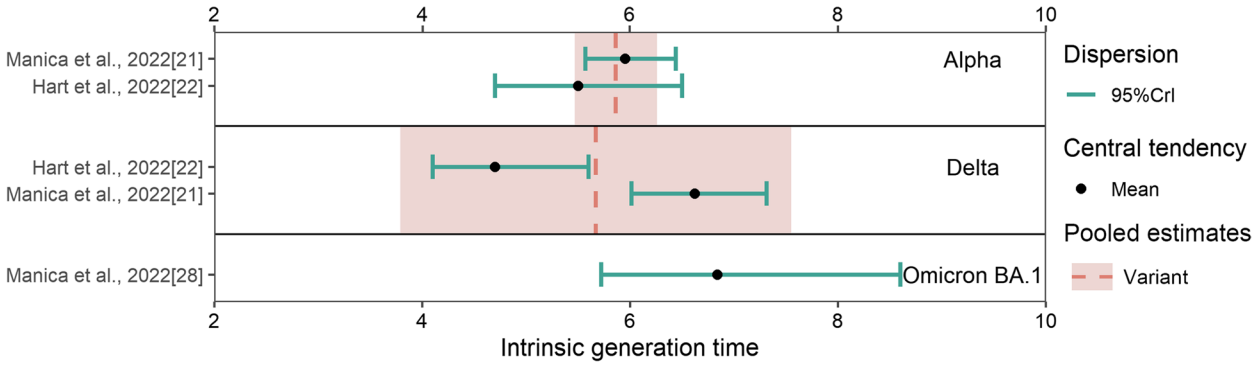

Fig. 6 The reported estimates of the intrinsic generation time. The red vertical dotted line and rectangle in different strata denote the pooled mean estimates and their 95% CI of corresponding variants, respectively. Black points and triangles represent mean estimates and median estimates, respectively. The horizontal segments indicate CrI (light blue)

are easier to obtain as they can more easily inferred from contact tracing and household studies than estimates for generation time, which requires more complex Bayesian analyses as the date of infection of the infector and their infectees are both generally unknown [21, 28]. Furthermore, China provided more records of estimates for the incubation period (60.6%), serial interval (34.6%), and generation time (37.5%) than any other country. This may be due to the smaller outbreak size of COVID-19 outbreaks in China before the rise of Omicron as compared to countries with widespread COVID-19 transmission, which made contact tracing and household studies easier to be conducted. This further supports the importance of contact tracing not only as a tool for monitoring and controlling infectious disease spread, but also for understanding transmission patterns.

Examining the intrinsic generation time is done using recently developed Bayesian methods, which may explain why only two studies have provided estimates for this indicator [22, 28]. Between these studies, there were only 5 records: 2 for Alpha, 2 the Delta, and 1 for Omicron BA.1. Given the small sample size, a pooled mean estimate was not warranted, and we could not compare possible differences between subsequent VOCs.

The incubation period of the ancestral lineage, and the Alpha, Beta, and Delta variants, is generally longer than that of other acute respiratory viral infections, such as human coronavirus (3.2 days), influenza

A (1.43–1.64 days), parainfluenza (2.6 days), respiratory syncytial virus (4.4 days), and rhinovirus (1.4 days) [258]. Our findings produced similar mean incubation period estimates to those reported by Du et al. for Delta (4.8 days 95% CI: 3.9–5.6) and Omicron (3.6 days, 95% CI: 2.3–4.9) [17] and those reported by Wu et al. for Alpha (5.00 days, 95% CI: 4.94–5.06 days), Delta (4.41 days, 95% CI: 3.76–5.05 days), and Omicron (3.42 days, 95% CI: 2.88–3.96 days) [16].

Our study showed that the mean serial interval of COVID-19 ranged from 1.7 to 7.5 days. These estimates are longer than those of influenza A(H3N2) (2.2 days) and pandemic influenza A(H1N1)pdm09 (2.8 days), but shorter than those of the respiratory syncytial virus (RSV, 7.5 days), measles (11.7 days), varicella (14.0 days), smallpox (17.7 days), mumps (18.0 days), rubella (18.3 days), pertussis (22.8 days), and Middle East respiratory syndrome (MERS, 7.6 days) [259, 260]. Our results were comparable to those of Du et al. who reported an average serial interval of 3.4 days (95%CI: 3.0-3.7) for the Delta variant and 3.1 days (95%CI: 2.9-3.2) for the Omicron variant, respectively [17]. The mean generation time of COVID-19 ranged from 2.36 to 6.84 days, longer than those of influenza A (H1N1) (2 days) and pandemic influenza A(H1N1)pdm09 (2.92 days) [261], but shorter than those of the MERS (10.7 days) [262, 263].

Our estimates are consistent with previous estimates for the incubation period and serial interval. However, despite more stringent inclusion criteria, our study conducted a more comprehensive database search than Du et al. [17] and Wu et al. [16] and analyzed more VOCs than Madewell et al. [18]. Our findings provide updated estimates, as they include both more recent and a greater number of estimates than were included in previous studies (Additional file 1: Table S5 [16–18]). Furthermore, previous reviews have not provided estimates for generation time, which is further stratified into intrinsic and realized generation time. Finally, by focusing on three time-to-key-event periods, our study provides a systematic comparison of how these mutually associated quantities evolved throughout the COVID-19 pandemic.

Overall, the serial interval maintained a shorter pooled mean estimate compared to the incubation period across different virus lineages, indicating that a large proportion of SARS-CoV-2 transmission occurs prior to symptom onset [180, 216]. Pre-symptomatic transmission was a critical factor facilitating SARS-CoV-2 spread [264], highlighting the importance of obtaining timely estimates of these indicators and keep monitoring their possible changes over the course of an epidemic.

The current study provides scientific evidence that the incubation period of COVID-19 has shortened as the virus has evolved, which has important implications for the formulation of effective epidemic control strategies such as isolation and quarantine. Vaccination has been shown to lead to reduced viral loads and duration of shedding of SARS-CoV-2, which varies with waning immunity [265]. Virus replication and shedding abilities are variant specific, which impact the duration of the incubation period [265, 266]. At the individual level, vaccination or infection status can affect the immune response to the virus, which would impact the estimates of the incubation period across different viral lineages [267, 268]. Furthermore, vaccination coverage and vaccine products vary between countries, which may impact the estimates of the incubation period for different study sites for the same viral lineage [269]. More research is needed to quantify the extent to which immunity affects the incubation period over time with consideration for individual-level heterogeneities as well as the effects of country-level heterogeneities of immunity on the incubation period for each VOC.

Our findings also demonstrated that the serial intervals of COVID-19 shortened with each new VOC. Previous studies have attributed decreased serial intervals to preventive measures that target the duration of potential transmission, such as isolation, contact tracing, quarantine, and other non-pharmaceutical interventions (NPIs) [11–14], which is further supported by the fact that longer serial intervals are often censored due to case isolations [31]. The highly heterogeneous implementation of NPIs between countries, within country, and time frame has probably contributed to heterogeneous estimates of the serial interval that we observed between studies. This applies also for estimates of the realized generation time.

We acknowledge some limitations in this study. When pooling the estimates across different virus lineages, we found considerable heterogeneities ($I^2 > 80\%$; I^2 refers to the percentage of total variation across studies that is due to heterogeneity rather than chance), possibly resulting from heterogeneities between the different study populations (e.g., deployed interventions, social behavior, demographic characteristics). Specifically, heterogeneities for the incubation period may be due to heterogeneities in the age structure and presence of pre-existing conditions in the host population [225, 270], whereas diversity in contact settings and the strength of NPIs may be responsible for heterogeneity of the estimates for the serial interval and realized generation time. Our analysis does not explore the observed heterogeneities because of the lack of harmonized data and information in the studies included in our meta-analysis. However, to incorporate these heterogeneities into the final estimates, we used random-effects models, as recommended by Deeks et al. [271]. This study may be limited by recall bias as many studies

included in the analysis rely on retrospective data collection for exposure and symptom onset, which would influence the obtained estimates. The incubation period for the Beta variant and the intrinsic generation time for Omicron were each included in only one study, and thus it was not possible to produce pooled estimates. Moreover, our analysis may be subject to bias due to the inclusion of studies from the early phase of the pandemic, which may potentially lead to an underestimation of the incubation period, as suggested by Xin et al. [193].

Conclusions

Our findings suggest that the incubation period, serial interval, and generation time of SARS-CoV-2 have evolved to shorter intervals with the emergence of each new VOC. Identifying the length of each of these indicators is critical for understanding the epidemiology of different SARS-CoV-2 variants and developing control measures for mitigating the spread of COVID-19. Moreover, understanding trends in these indicators can be instrumental for preparedness planning for future COVID-19 outbreaks.

Abbreviations

CI	Confidence interval
CrI	Credible interval
IQR	Interquartile range
VOC	Variant of concern

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-023-03070-8.

Additional file 1: Table S1. Search strategy and search results. **Table S2.** Quality assessment scale. **Table S3.** Excluded studies and reason for exclusion. **Table S4.** Quality assessment of the studies used in the meta-analysis. **Figure S1.** Forest plot for studies of reporting estimates of the incubation period for different SARS-CoV-2 lineages. **Figure S2.** Funnel plot for the incubation period with a 95% CI for studies included in the meta-analysis. **Figure S3.** Forest plot for studies of reporting estimates of the serial interval for different SARS-CoV-2 lineages. **Figure S4.** Funnel plot for the serial interval with a 95% CI for studies included in the meta-analysis. **Figure S5.** Forest plot for studies of reporting estimates of the realized generation time for different SARS-CoV-2 lineages. **Figure S6.** Funnel plot for the realized generation time with a 95% CI for studies included in the meta-analysis. **Figure S7.** Forest plot for studies of reporting estimates of the intrinsic generation time for different SARS-CoV-2 lineages. **Table S5.** Characteristics of previous meta-analyses of the incubation period and/or serial interval of SARS-CoV-2 VOCs.

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Authors' contributions

MA, YPW, YW, and HL conceived and designed the study. HY and MA supervised the study. XX, YPW, YZ, and ZH participated in data collection. XX and YPW participated in statistical analysis. XX and YZ prepared the tables and figures. YPW, AGK, and XX drafted the manuscript. MA, AGK, and YPW revised the content critically. All authors read and approved the final manuscript.

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Availability of data and materials

The dataset generated and analyzed in the current study are available online at https://github.com/xxyy0574/COVID-19-transmission-parameters.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

HY has received research funding from Sanofi Pasteur, GlaxoSmithKline, Yichang HEC Changjiang Pharmaceutical Company, Shanghai Roche Pharmaceutical Company, and SINOVAC Biotech Ltd. MA has received research funding from Seqirus. None of those funding is related to this research. All other authors report no competing interests.

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